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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/554,567	09/01/2000	Adriano Aguzzi	6458.US.01	2914

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EXAMINER	
WINKLER, ULRIKE	
ART UNIT	PAPER NUMBER
1648	24

DATE MAILED: 02/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/554,567	AGUZZI ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler, Ph.D.	1648	

-- The MAILING DATE of this c mmunication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 December 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *19* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Request for Continued Examination

The request filed on December 9, 2002 (Paper No. 21) for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/554,567 is acceptable and a RCE has been established. Claims 35-40 have been amended (Paper No. 22) are pending and are currently under prosecution. An action on the RCE follows.

Applicant's amendments, filed Paper Nos. 5, 8, 16 and 22, are acknowledged.

Claims 1-28 have been canceled, in Paper No. 8 (6/9/2001)

Claims 32-34 have been added, in Paper No. 8 (6/9/2001)

Claims 29-34 have been canceled in Paper No. 16 (3/16/2002)

Claims 35-40 have been added in Paper No. 16 (3/16/2002)

Claims 35-40 have been amended in Paper No. 22 (12/9/2002)

The Art Unit location and Examiner of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to **Art Unit 1648, Examiner Ulrike Winkler**.

Priority

The office acknowledges the amendment to the specification (Paper No. 16) to indicate that priority is claimed under 35 U.S.C. 371 to PCT/EP98/08271.

Information Disclosure Statement

An initialed and dated copy of Applicant's IDS form 1449, Paper No. 19, is attached to the instant Office action.

Specification

The Office acknowledges the receipt and entry of an abstract on a separate sheet in Paper No. 16.

The Office acknowledges the amendment to the title in Paper No. 16.

Drawings

The Office acknowledges the receipt of the formal drawings in Paper No. 19, the drawings have been approved by the Draftsperson.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 35-40 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is **withdrawn** in view of Applicants amendments to the claims.

(New Rejection) The term "TSE-infected B-cell antigen" or "TSE-infected T-cell antigen"" in claims 35-40 is a relative term which renders the claim indefinite. The term ""TSE-infected B-cell antigen" or "TSE-infected T-cell antigen"" is not defined by the claims, the specification

does not provide a standard for ascertaining the structure of the antigen, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The instant claims a method of identifying TSE in a B or T cell. The method requires the utilization an antibody, the antibody production method described in Examples 4 and 5 would not produce an antibody profile that can distinguish between a TSE-infected B or T cell and a normal B or T cells (see 112-1st paragraph rejection below). The antibody production procedure utilizes lysates from TSE-infected T or B cells, these lysates will contain all proteins in a B or T cell including normal prion protein as well as the infectious prion protein. The prior art has shown that immunizing a PrP 0/0 mouse with an infectious prion protein will not result in antibodies that only recognize the infectious prion conformation of the protein. The antibodies in the prior art also recognize the normal prion protein conformation. The infectious prion protein has the same amino acid structure as the normal prion protein. B or T cells from the buffy coat of blood contain normal prion protein (Bendheim et al.; Neurology, IDS Paper No. 15, specifically see page 151, column 1, last paragraph,) presenting a piece of the prion protein in context of B or T cell surface receptors would not result in a structural distinction between a TSE-infected B or T cell antigen. Therefore, the term "TSE-infected B-cell antigen" or "TSE-infected T-cell antigen" is indefinite.

For purposes of the instant Office action the term "TSE-infected B-cell antigen" or "TSE-infected T-cell antigen" is interested to be an antibody that can determine the difference between an infectious prion conformation (TSE) and the normal cellular form.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. To comply with the written description requirement of 35 U.S.C. § 112, first paragraph, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention and all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the invention. This may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was complete by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. The present application contains no disclosure of a specific antibody which would be able to distinguish specific structures for "TSE-infected B-cell antigen" or a "TSE-infected T-cell antigen". The specification merely provides prophetic examples of how to go about producing a ligand/ antibody to a prion infected B or T cell. The specification does not provide a single antibody that is able to identify a TSE-infected B-cell from a normal B-cell that contain the normal prion protein. The specification does not provide a sufficient written description that would provide the requisite road map to obtain the claimed antibody. The prion protein has minimally two

different conformational structures one is primarily alpha helical while the other form attains a beta-sheet conformer, both conformers have the same amino acid sequence. Therefore, based on the instant specification is not clear that applicant was in possession of a an antibody that binds "TSE-infected B-cell antigen" and/or a "TSE-infected T-cell antigen", these antibodies are required to perform the method steps set out in the claims.

Claims 35-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification provides a prophetic example of obtaining and antibody that recognizes a "TSE-infected B-cell antigen" and/or a "TSE-infected T-cell antigen". The specification does not provide a single example of an antibody produced by the described methods that is able to distinguish between a "TSE-infected B-cell antigen" and/or a "TSE-infected T-cell antigen".

Instant claims are evaluated for enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows: (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims. The Wands factor analysis, such an analysis does not need to be specifically enumerate (points 1-8) but only needs to have a select few of the factors present discussed in a rejection. In order to show

applicant that the appropriate factors have been taken into account, an enumerated Wands analysis follows.

(1) the nature of the invention, requires an antibody for the method steps; however, the antibody production method described in Examples 4 and 5 of the specification would not produce an antibody profile that can distinguish between an TSE-infected B or T cell and a normal B or T cells. The procedure utilizes lysates from infected TSE-T or B cells, these lysates will contain all proteins in a B or T cell including normal prion protein as well as the infectious prion protein. (2) the state of the prior art, has shown that immunizing a PrP 0/0 mouse with an infectious prion protein will not result in antibodies that recognize the infectious prion form only [see Williamson et al.; IDS Paper No. #19, pages 7279-7282, specifically see page 7281, column 2, lines 8-11]. The antibodies in the prior art will also recognize the normal prion protein conformation. Hence injecting a B or T-cell lysate from a TSE-infected animal will not produce antibodies that are specific for TSE-infected B or T cells. Because infectious prion proteins have the amino acid structure as normal prion protein a B or T-cell presenting a piece of the prion protein in context with their cell surface receptors would not be distinguishable form a B or T-cell that is not infected and contain only the cellular form of the prion protein (see Bendheim et al.; Neurology, IDS Paper No. 15). (3) the predictability or lack thereof in the art; the difficulty presented in the prior art to in the efforts to produce antibodies that are specific for the infectious form the prion protein indicates that there is a great lack of predictability in generating antibodies to proteins that have more than on conformational state. This falls outside the dogma that a single polypeptide sequence will attain a single three dimensional structure. (4) the amount of direction or guidance present, the specification provides no guidance or direction to overcome

the difficulties of the prior art in achieving the goal of producing antibodies that can distinguish between the infectious and normal conformer of the prion protein. (5) the presence or absence of working examples, the specification has provided not antibodies that recognize specific structure that are unique to a TSE-infected B or T cell. (6) the quantity of experimentation necessary, it would require undue experimentation to obtain antibodies that can be utilized in the claimed method steps. (7) the relative skill of those in the art, is high. (8) the breadth of the claims, greatly reduces the probability that one of skill in the art would successfully obtain the claimed invention without undue experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 35-40 under 35 U.S.C. 102(b) as being anticipated by Kuroda et al. (Infection and Immunity 1983; 41:154-61) **is withdrawn** in view of Applicants amendments to the claims.

The rejection of claims 32-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Manuelidis et al. (Science 1978; 200:1069-1071) **is withdrawn** in view of Applicants amendments to the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 35-40 under 35 U.S.C. 103(a) as being unpatentable over O'Rourke et al (US Pat No. 6,165,784),and/or Korth et al. (Nature 6 November 1997; 390:74-77), in view of Kuroda et al. (Infection and Immunity 1983; 41:154-61) and/or Manuelidis et al. (Science 1978; 200:1069-1071) **is maintained** for reasons of record.

Applicants arguments have been fully considered but the have failed to persuade the Office to remove the instant rejection. Because it is not clear what specific structure is recognized by an antibody to a "TSE-infected B-cell antigen" and/ or a "TSE-infected T cell antigen" (see 112 2nd paragraph rejection above), for purposes of the instant rejection the claims are interpreted to read on antibodies that can recognize the infectious prion protein conformer.

The claims are broadly drawn to methods for the identification of the presence of transmissible spongiform encephalopathy (TSE) in B cells and/or T cells. The method steps are interpreted broadly (comprising) indicating that the methods may have more steps than those enumerated in the claims, such as an unmasking step of the epitope.

O'Rourke et al. teach methods to test for transmissible spongiform encephalopathy in lymphoid tissue using an antibody that serves as a ligand in various immunoassays, including immunohistochemistry, western immunoblots, and dot blots (see entire document, e.g., "Summary of the Invention"). O'Rourke et al. teach that antibody ligands may be either polyclonal sera or monoclonal antibodies (see entire document, e.g., column 5, especially lines 40-50). O'Rourke et al. also teach the importance of developing tests that allow non-invasive preclinical evaluation of animals suspected of being infected with TSE, versus the standard approach of assaying brain biopsy material (see entire document, including the "Background of the Invention", especially the summary statement at column 3, lines 27-31).

Korth et al. teach a method of detecting transmissible spongiform encephalopathy based upon a monoclonal antibody that is specific for the prion form of PrP (the causative agent in TSEs) versus the cellular form of PrP (see entire document, e.g. Abstract). Korth et al. teach that this antibody can be used to identify the prion form of PrP directly, thus providing a basis for a TSE test in living humans or animals, by lowering the detection threshold needed (see especially paragraph preceding "Methods" on page 77).

Neither O'Rourke et al. or Korth et al. teach collecting B cells and/or T cells from a test sample and directly testing these cell types for the presence of transmissible spongiform encephalopathy.

Kuroda et al. teach that fractionated B cells and T cells obtained from the spleens of mice infected with the causative agent of Creutzfeldt-Jakob disease (CJD), a form of transmissible spongiform encephalopathy (TSE), can be injected into susceptible mice and transmit disease (see entire document, especially Tables 2 and 4). Thus Kuroda et al. teach a method to test for the presence of transmissible spongiform encephalopathy comprising obtaining a sample of spleen, collecting B cells and collecting T cells from the sample, and testing the B cells and/or T cells for the presence of transmissible spongiform encephalopathy. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties in the method taught by Kuroda et al.

Manuelidis et al. teach a method to test for the presence of transmissible spongiform encephalopathy comprising obtaining a sample of whole blood (which is a heterogeneous mixture of cell types and other components), collecting B cells and collecting T cells from the sample by isolating the buffy coat, and testing the B cells and T cells contained within the buffy coat for the presence of transmissible spongiform encephalopathy. Manuelidis et al. attribute their ability to demonstrate the infectivity of blood to an increase in the sensitivity of the assay made possible by collecting a specific fraction of whole blood (that inherently containing the B cells and T cells) (see entire document, especially the last full paragraph on page 1070). The ability to transmit disease to another animal is a well established means of testing for the presence of an infectious agent. Since the white blood cells of the buffy coat of whole blood are inherently B cells and T cells. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties in the method taught by Manuelidis et al.

Thus Kuroda et al. teach that both B cells and T cells can transmit TSE, and Manuelidis et al. teach that it is important to focus on these cellular populations to increase the sensitivity of assays for TSE infectivity. Both O'Rourke et al. and Korth et al. teach that sensitive tests for TSEs are provided by antibody-based assays. And O'Rourke et al. further point out that sampling and testing samples containing lymphocytes is a relatively non-invasive to the animal to be tested. Thus one of ordinary skill in the art at the time the invention was made would have found it obvious to improve the sensitivity of the TSE tests by collecting samples containing B cells and/or T cells and testing for the presence of TSE by using an antibody-based system. The ordinary artisan at the time the invention was made would have been motivated to test B cells and/or T cells for the presence of TSE using antibodies since this sort of test method utilized a sensitive reagent/ligand, antibodies; to assay cell types that were easily obtainable by non-invasive methods from living animals, in contrast to the other art-recognized approach of brain biopsy. The ordinary artisan at the time the invention was made would have reasonably expected that, as taught by Manuelidis, focusing on a cell type known to be infectious would increase the sensitivity of detection assays, including antibody-based assays. In addition, it was well known in the art at the time the invention was made that once an antibody was developed, the antibody could be used with a reasonable expectation of success to detect an antigen on intact cells, as in a buffy coat of whole blood, by either mounting them on slides for immunohistochemical analysis; or by using other techniques well known in the art at the time the invention was made for intact cell analysis with antibodies. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 or for informal communications use 703-308-4426.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ulrike Winkler, Ph.D.

James C. Housel 2/23/03
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